

wherein said process comprises the steps of: (a) at least partially melting said [ancillary substance] ingredient, (b) mixing at least one of said CO₂ donor and said acidic component with said at least partially melted [ancillary substance] ingredient to form an at least partially molten blend, (c) cooling said at least partially molten blend, (d) combining said at least partially molten blend, said pharmaceutically active substance and any remaining portion of said effervescent system and (e) forming said stabilized medicament.

REMARKS

The claims have been amended to correct inadvertent errors and to clarify the scope of the invention under 35 U.S.C. § 112. No reduction in the scope of the claims, either express or implied, is intended, and no reduction of the scope of the claims should be inferred.

The claimed invention covers effervescent compositions with improved stability and methods of making these compositions. Applicant has discovered that incorporating at least one member of the effervescent couple in a dispersion of a fusible sugar, sugar alcohol or sugar substitute improves product stability.

In the Examiner's Advisory action of August 29, 2002, the Examiner ruled that the amended claims did not put the case in condition for allowance for three reasons, as set forth more fully below. Applicant respectfully traverses the Examiner's rejections,

especially as related to the amended claims set forth herein, and requests allowance of the claims.

1. KHANKARI CANNOT ANTICIPATE BECAUSE IT DOES NOT TEACH MELTING.

In the Final Office Action in this case, the Examiner had rejected claims 8-10, citing Example 1 and column 14, lines 44-65 of U.S. Patent No. 6,024,981 to Khankari et al. (“Khankari”). Applicant responded to the Examiner’s position by noting the distinction between the structure found in the claimed dispersion of the invention and the structure contemplated by Khankari’s direct compression of ingredients. This difference in structure alone distinguished the invention from the Khankari structure. Applicant argued that the relatively low compression strength of Kahnkari (20-50N) does not form a melt of a fusible sugar, sugar alcohol or sugar substitute sufficient to form the dispersion required in the claimed invention.

In the Advisory Action, the Examiner rejected applicant’s arguments, saying that applicants had not claimed a melting step, that the direct compression of Khankari causes melting to occur, and that applicant’s arguments to the contrary are mere opinion.

(A) APPLICANT HAS CLAIMED A “MELTING” STEP.

Contrary to the Examiner’s assertion, however, applicant has claimed a structure formed by a melt. Applicant has revised claim 8 to emphasize the nature of the

dispersion and to make the claim more clear to the Examiner. Other techniques may give the structure found in claim 8, so claim 8 is not a “product by process” claim that is confined to a melting step that forms the structure. Nevertheless, melting of the substrate is indeed one way to disperse at least one of the acid/base couple into the substrate as part of a solidified solution, suspension or emulsion.

(B) NOTHING IN KHANKARI MENTIONS MELTING.

Khankari is silent on melting. Khankari is silent on temperature. The only reasonable inference to draw from this silence is that the direct compression described in Khankari takes place at room temperature and that melting is not a significant problem. Indeed, it only makes sense that significant melting should *not* take place in tablet formation through direct compression. The melted materials would have to re-solidify, and, in the absence of cooling equipment, could be expected to deform the shape of the tablet. Such deformation would cause problems with subsequent processing and handling. Khankari would have noted and dealt with such an apparent defect. Since Khankari did not address the problem, the problem must not have existed. So, the tablet in Khankari did not melt.

Tablet presses, which are used for direct compression of tablets, differ from extruders, such as those mentioned in Example 1 of the patent application. Tablet presses are generally not heated and tablets produced by tablet presses do not generally require cooling. On the other hand, the extruded material of Example 1 of the application is

heated to 80° C. The extrudate is cooled before subsequent processing. The absence of heating and cooling equipment for ordinary tablet presses further suggests that direct compression, particularly at the low pressures contemplated by Khankari, dies not produce the structure of claim 8.

(C) THE EXAMINER MUST SHOW THAT KHANKARI NECESSARILY PRODUCES A MELT.

Under MPEP 2112, if the cited art is silent as to a characteristic or property, a rejection under section 102 can only be made when the Examiner has provided a rationale or evidence tending to show inherency of that characteristic or property. In this application, inherency requires a rationale or evidence that melting *necessarily* occurs in Khankari. The Examiner has not yet shown that melting could reasonably be expected to result from the process set forth in Khankari. Thus, there is no inherency proof to rebut, and the Examiner should withdraw the rejection.

2. LESLIE'S SUGARS ARE NOT THE "MATRIX" RELIED UPON BY THE EXAMINER.

In the Final Office Action, the Examiner rejected the process claims under 35 U.S.C. § 102 (b), based on UK Patent No. 2,307,857 to Leslie et al. ("Leslie"). The Examiner argued that an effervescent couple, an active agent and a sweetener are disclosed in Leslie as well as granulation and extrusion. Applicant responded to this rejection by pointing out that stability is not the objective of Leslie and that the amount of sweetener in Leslie is not sufficient to form a dispersion.

In the Advisory Action, the Examiner argued that Leslie shows an acid/base couple dispersed in a matrix at page 2, paragraph 3, so the sugars of Leslie must meet the claimed limitation.

This argument is respectfully traversed. Leslie describes, (at Page 2, paragraph 3) that in *one* embodiment, but not the *only* embodiment, the acid/base couple may be dispersed in a matrix comprising *polyethylene glycol (PEG)* of molecular weight 1,000 to 20,000. The sugar substitutes in Leslie are discussed at page 2, paragraph 4, and are described as “usual excipients.” Thus, only Example 3 of Leslie reports a matrix, even though all three examples have saccharin. That matrix is polyethylene glycol 6000.

The Examiner’s argument that the saccharin of the Leslie examples is a matrix for the acid/base couple inverts the relationship among the ingredients. The weight ratio of saccharin to the acid/base ingredients in the Leslie examples is set forth in Table 1:

Table 1 – Weight Ratio of Saccharin to Acid/Base Ingredients in <u>Leslie</u> Examples			
Example	Saccharin Weight in Mg	Acid/Base Ingredients in Mg	Weight Ratio
1	5.0	2,233.0	1:446.6
2	2.5	1,116.5	1:446.6
3	2.5	1,116.5	1:446.6

A weight ratio of almost 1:500 cannot be a dispersion of acid/base ingredients in saccharin. If there is a dispersion, then the saccharin is dispersed in the acid/base

materials, not vice-versa. By analogy, a 1:500 ratio of water to oil does not make an oil-in-water emulsion. It would make a water-in-oil emulsion.

3. LESLIE DOES NOT REQUIRE MELTING.

Granulation is not inherently a process for producing a dispersion by melting. Rather, granulation at best softens the outer portion of a substrate so that a second material may adhere to its surface.

Attached hereto is a copy of a Material Safety Data Sheet for polyethylene glycol 6000 that applicant downloaded off the Internet. Item 9 of that MSDS shows the melting point for PEG 6000 as 56-63° C (the relevant portion has been highlighted). Thus, the PEG 6000 is not necessarily melted, and, if any melting takes place, that melting may be only partial, surface melting that allows adhesion of particles to the surface of the PEG 6000 granules, not formation of a dispersion within a melt. Moreover, regardless of what happens later in processing in Leslie, including extrusion, Leslie does not specify conditions under which a substantial amount of saccharin could be melted.

In view of the arguments set forth above and the claim amendments presented herein, Applicants respectfully submit that the pending claims are in condition for allowance. Reconsideration is respectfully requested. The Examiner is invited to call the undersigned attorney at 973 408-8229 with any questions.

Respectfully Submitted,



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